IN THE MATTER OF an Application
for a German Patent
filed under 102 55 681.4, and
IN THE MATTER OF an Application
for Patent in U.S.A.
filed under No. 10/535,474

I, Dr. Dietmar Forstmeyer,
attorney to BOETERS & LIECK, of Oberanger 32, D-80331 Muenchen, Germany, do solemnly and sincerely declare that I am conversant with the English and German languages and am a competent translator thereof, and that the following is, to the best of my knowledge and belief, a true and correct translation of the German Patent Application filed under 102 55 681.4 by R & D Pharmaceuticals GmbH.

DECLARED:

THIS 6th DAY OF August 2007

D. Forstmeyer

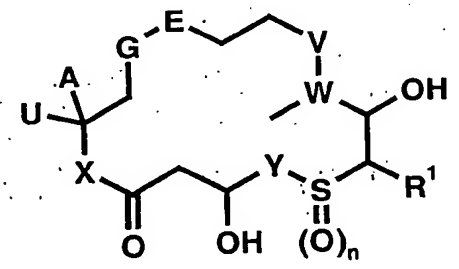
Dr. Dietmar Forstmeyer

Novel Macrocycles for the treatment of cancer

Epothilones (DE4138042) are natural products with extraordinary biological activity, e.g. as inhibitors of mitosis, microtubuli-modifying agents, cytotoxica or fungizides. Especially, they possess Paclitaxel-like properties and exceed Paclitaxel (Taxol®) in some tests in activity. Some derivatives are currently undergoing clinical trials for the cure of cancer diseases (Nicolaou et al. Angew. Chem. Int. Ed. 1998, 37, 2014-2045; Flörsheimer et al. Expert Opin. Ther. Patents 2001, 11, 951-968).

The object of the present invention was to provide new epothilone-like derivatives having an improved profile regarding their preclinical and clinical development potential.

The present invention relates to compounds of general Formula (I):



(I)

wherein

A is a heteroalkyl, a heterocycloalkyl, a heteroalkylcycloalkyl, a heteroaryl or a heteroarylalkyl residue,

U is a heteroalkyl, a heterocycloalkyl, a heteroalkylcycloalkyl, a heteroaryl or a heteroarylalkyl residue,

G-E is selected from the following groups,

or is part of an optionally substituted phenyl ring,

n is 0 or 2,

R^1 is a C_1-C_4-alkyl, or a C_3-C_4-cycloalkyl group,

V-W is a group of formula CH_2CH or CH=C,

X is an oxygen atom or a group of formula NR^2, wherein R^2 is a hydrogen atom, an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or a heteroarylalkyl residue and

Y is a group of formula CR^3R^4, wherein R^3 and R^4 independently from each other are a hydrogen atom, a C_1-C_4-alkyl group or together are part of a cycloalkyl group with 3 or 4 ring atoms,

or a pharmacologically acceptable salt, solvate, hydrate or a pharmacologically acceptable formulation thereof.

The term alkyl refers to a saturated straight or branched chain hydrocarbon group, containing from one to 20 carbon atoms, preferably from one to 12 carbon atoms, especially preferably one to 6 carbon atoms, e.g. the methyl, ethyl, iso-propyl, iso-butyl, tert.-butyl, n-hexyl, 2,2-dimethylbutyl, n-octyl, allyl, isoprenyl or hexa-2-enyl group.

The terms alkenyl and alkynyl refer to at least partially unsaturated straight or branched chain hydrocarbon groups, containing from two to 20 carbon atoms, preferably from two to 12 carbon atoms, especially preferably two to 6 carbon atoms, e.g. the allyl, acetylenyl, propargyl, isoprenyl or hexa-2-enyl group.

The term heteroalkyl refers to an alkyl, an alkenyl or an alkynyl group wherein one or more (preferrably 1, 2 or 3) carbon atoms are replaced by an oxygen, nitrogen, phosphorous, boron or sulphur atom (preferrably oxygen, sulphur or nitrogen), e.g. an alkoxy group like e.g. methoxy or ethoxy, or a methoxymethyl, nitril, methylcarboxyalkyl-ester or 2,3-dioxyethyl group. The term heteroalkyl furthermore refers to a carboxylic acid or a group derived from a carboxylic acid like e.g. acyl, acyloxy, carboxyalkyl, carboxyalkyl ester e.g. methyl carboxyalkyl ester, carboxyalkyl amide, alkoxycarbonyl or alkoxycarbonyl-oxy.

The expression cycloalkyl or cyclo- refers to a saturated or partially unsaturated cyclic group which has one or more

rings forming a structure containing from 3 to 14 carbon atoms, preferably from 3 to 10 carbon atoms, for example a cyclopropyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl or cyclohex-2-enyl group.

The expression heterocycloalkyl or heterocyclo- refers to a cycloalkyl group as defined above in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus or sulphur atom and can be, for example, the piperidine, morpholine, tetrahydrofuran, tetrahydrotiophen, N-methylpiperazine or N-phenylpiperazine group.

The terms alkylcycloalkyl or heteroalkylcycloalkyl refer to groups comprising, in accordance with the above definitions, both cycloalkyl or heterocycloalkyl respectively, and also alkyl, alkenyl, alkynyl and/or heteroalkyl groups.

The expression aryl or Ar refers to an aromatic group which has one or more rings and is formed by a structure containing from 5 to 14 carbon atoms, preferably 5 or 6 to 10 carbon atoms, for example a phenyl, naphthyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 4-carboxyphenyl-alkyl or 4-hydroxyphenyl group.

The expression heteroaryl refers to an aryl group in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus or sulphur atom, for example the 4-pyridyl, 2-imidazolyl, 3-pyrazolyl, oxazolyl, thiazolyl, thiophenyl and isoquinolyl group.

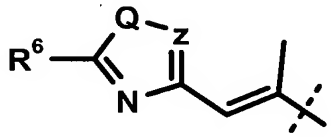
The expressions aralkyl and heteroaralkyl refer to groups comprising, in accordance with the above definitions, both aryl or heteroaryl, respectively, and also alkyl, alkenyl, alkinyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups, for example, the tetrahydroisoquinolyl, benzyl, 2- or 3-ethyl-indolyl or 4-methyl-pyridino group.

The expressions alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl and also "optionally substituted" refer also to groups in which one or more hydrogen atoms of such groups have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH_2 or NO_2 groups. Those expressions refer furthermore to groups substituted by unsubstituted alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl groups.

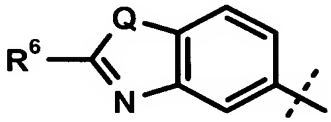
Owing to their substitution, compounds of formula (I) may contain one or more centres of chirality. The present invention therefore includes both all pure enantiomers and all pure diastereoisomers and also mixtures thereof in any mixing ratio. Furthermore, the present invention also includes all cis/trans isomers of compounds of general formula (I) and also mixtures thereof.

Preferred are compounds of formula (I), wherein A is a group of the formula $-C(CH_3)=CHR^5$ or $-CH=CHR^5$, wherein R^5 is a heteroaryl or a heteroarylalkyl residue.

Further preferred are compounds of formula (I), wherein A shows the general formula (II) or (III):



(II)



(III)

wherein Q is a sulphur atom, an oxygen atom or a group of formula NR^7, wherein R^7 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 heteroalkyl group, z is a nitrogen atom or a CH group and R^6 is a group of formula OR^8 or NHR^8, an alkyl, alkenyl, alkynyl or a heteroalkyl group (preferably a group of formula CH_2OR^8 or CH_2NHR^8), wherein R^8 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 heteroalkyl group (especially a hydrogen atom).

Especially preferred, z is a CH group.

Again preferred are compounds of formula (I) wherein Q is a sulphur atom or an oxygen atom.

Especially preferred are compounds of formula (I) wherein R^6 is a group of formula CH_3, CH_2OH or CH_2NH_2.

Further preferred, R^2 is a hydrogen atom or a C_1-C_4 alkyl group (especially preferred a hydrogen atom).

Further preferred are compounds of formula (I), wherein X is an oxygen atom.

Moreover, R^1 preferably is a methyl or an ethyl group; especially preferably a methyl group.

Again preferred, Y is a group of formula $C(CH_3)_2$.

Moreover preferred, U is a group of formula COOH or a hydrogen atom; especially preferred, U is a hydrogen atom.

Examples of pharmacologically acceptable salts of compounds of formula (I) are salts (or mixed salts) of physiologically acceptable mineral acids, such as hydrochloric acid, sulphuric acid and phosphoric acid; or salts of organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, lactic acid, acetic acid, trifluoroacetic acid, citric acid, succinic acid, fumaric acid, maleic acid and salicylic acid. Compounds of formula (I) can be solvated, especially hydrated. The hydration may take place, for example, during the preparation process or as a consequence of the hygroscopic nature of the initially anhydrous compounds of formula (I). If the compounds of Formula (I) contain asymmetric C-atoms they may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds. Furthermore, the present invention also includes all cis/trans isomers of the

present compounds of general formula (I) and also mixtures thereof.

The pharmaceutical compositions according to the present invention comprise at least one compound of formula (I) as active ingredient and optionally carrier substances and/or adjuvants.

The pro-drugs (see, e.g. R. B. Silverman, Medizinische Chemie, VCH Weinheim, 1995, Chapter 8, S. 361ff), which are also an object of the present invention, consist of a compound of formula (I) and at least one pharmacologically acceptable protecting group that is removed under physiological conditions, for example an alkoxy, aralkyloxy, acyl or acyloxy group, such as, for example, an ethoxy, benzyloxy, acetyl or acetyloxy group.

The therapeutic use of the compounds of formula (I), of their pharmacologically acceptable salts and solvates and hydrates and also formulations and pharmaceutical compositions also lies within the scope of the present invention.

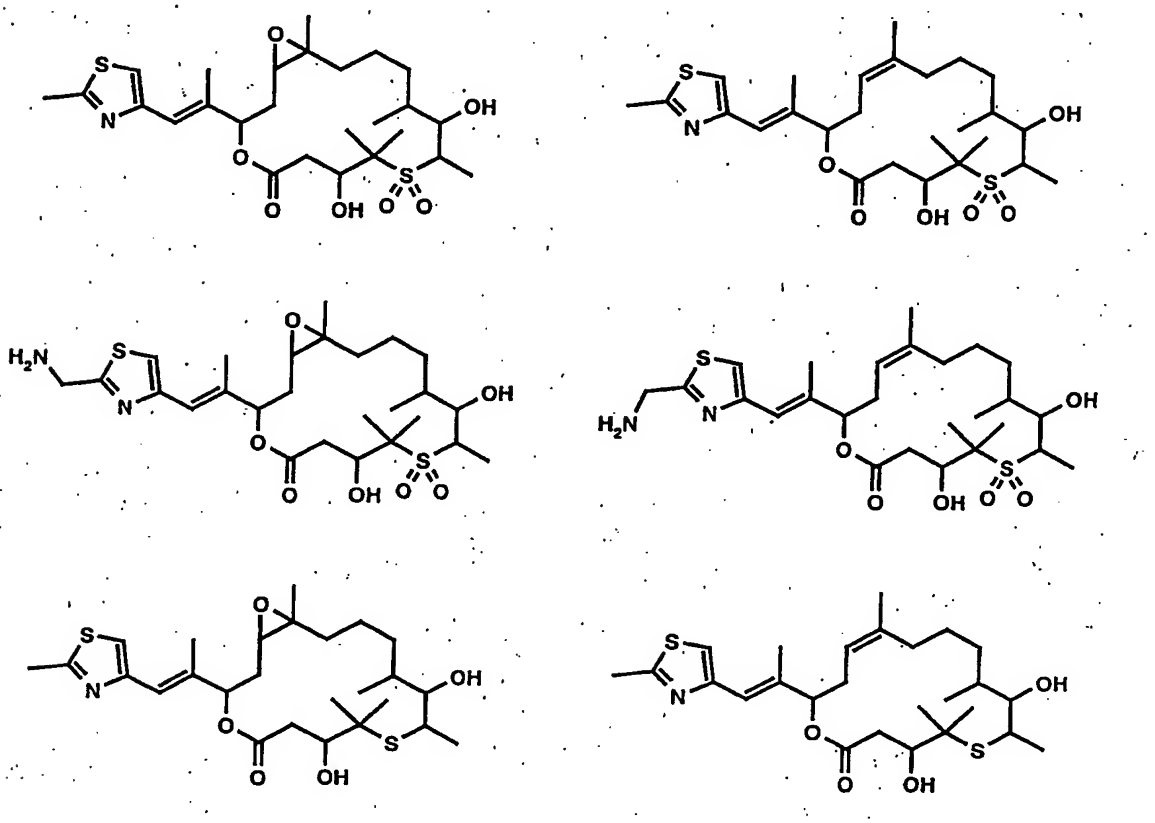
The use of those active ingredients in the preparation of medicaments for the treatment of cancer diseases is also an object of the present invention. In general, compounds of Formula (I) will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of

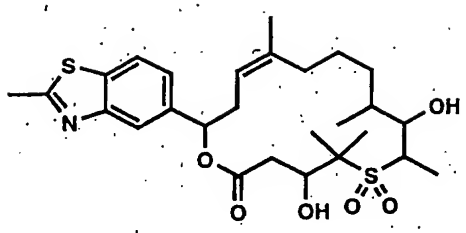
the following routes: oral, e.g. as dragees, coated tablets, pills, semisolids, soft or hard capsules, solutions, emulsions or suspensions; parenteral e.g. as an injectable solution; rectal as suppositories; by inhalation e.g. as a powder formulation or spray, transdermal or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard gelatin capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients e.g. with lactose, sucrose, glucose, gelatin, malt, silica gel, starch or derivatives thereof, talc, stearic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as e.g. vegetable oils, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions and syrups one may use excipients as e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, vegetable oils, petroleum, animal or synthetic oils. For suppositories one may use excipients as e.g. vegetable oils, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as e.g. oxygen, nitrogen, noble gases and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilization, emulsifiers, sweeteners, flavourings, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

Combinations with other therapeutic agents may include other therapeutically useful agents that are commonly used to treat cancer diseases.

For the treatment of cancer diseases the dose of the biologically active compound according to the present invention may vary within broad limits and can be adjusted to the individual needs. In general a dose of 0.1 microgram to 100 milligram per kilogram body weight per day is appropriate, with a preferred dose of 10 micrograms to 25 milligrams/kilogram per day. In appropriate cases the dose may be also higher or lower than given above.

Examples

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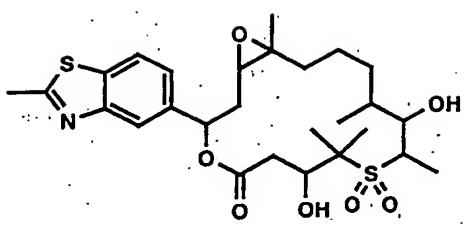
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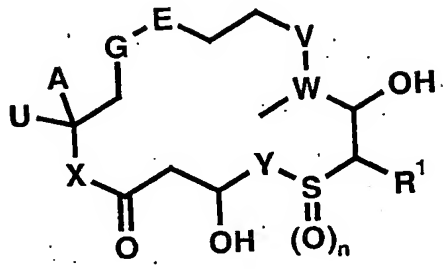
Claims

1. Compounds of general Formula (I)



(I)

wherein

A is a heteroalkyl, a heterocycloalkyl, a heteroalkyl-cycloalkyl, a heteroaryl or a heteroarylalkyl residue,

U is a heteroalkyl, a heterocycloalkyl, a heteroalkylcycloalkyl, a heteroaryl or a heteroarylalkyl residue,

G-E is selected from the following groups,

or is part of an optionally substituted phenyl ring,

n is 0 or 2,

R^1 is a C_1-C_4-alkyl or a C_3-C_4-cycloalkyl group,

V-W is a group of formula CH_2CH or CH=C,

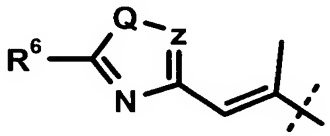
X is an oxygen atom or a group of formula NR^2, wherein R^2 is a hydrogen atom, an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroarylalkyl residue and

Y is a group of formula CR^3R^4, wherein R^3 and R^4 independently from each other are a hydrogen atom, a C_1-C_4-alkyl group or together are part of a cycloalkyl group with 3 or 4 ring atoms,

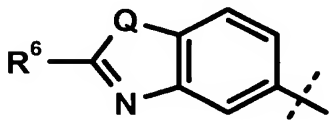
or a pharmacologically acceptable salt, solvate, hydrate or a pharmaceutically acceptable formulation thereof.

2. Compounds according to claim 1, wherein A is a group of formula $-C(CH_3)=CHR^5$ or $-CH=CHR^5$, wherein R^5 is a heteroaryl or a heteroarylalkyl group.

3. Compounds according to claim 1, wherein A shows the general formula (II) or (III)



(II)



(III)

wherein

Q is a sulphur atom, an oxygen atom or a group of formula NR^7, wherein R^7 is a hydrogen atom, a C_1-C_4 alkyl

group or a C_1-C_4 heteroalkyl group, z is a nitrogen atom or a CH group and R^6 is a group of formula OR^8 or NHR^8, an alkyl-, alkenyl, alkynyl or a heteroalkyl group, wherein R^8 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 heteroalkyl group.

4. Compounds according to claim 3, wherein z is a CH group.

5. Compounds according to claims 3 or 4, wherein Q is a sulphur atom or an oxygen atom.

6. Compounds according to anyone of claims 3 to 5, wherein R^6 is a group of formula CH_3, CH_2OH or CH_2NH_2.

7. Compounds according to anyone of claims 1 to 6, wherein U is a hydrogen atom.

8. Compounds according to anyone of claims 1 to 6, wherein X is an oxygen atom.

9. Compounds according to anyone of claims 1 to 8, wherein R^1 is a methyl group.

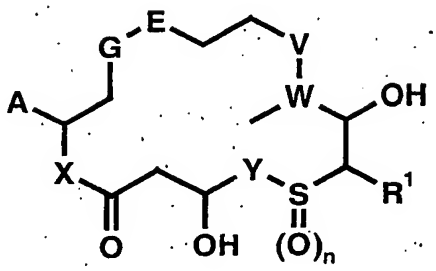
10. Compounds according to anyone of claims 1 to 9, wherein Y is a group of formula $C(CH_3)_2$.

11. Pharmaceutical composition containing a compound according to anyone of claims 1 to 10 and optionally carriers and/or adjuvants.

12. Use of a compound or a pharmaceutical composition according to any one of claims 1 to 11 for the treatment of cancer diseases.

Abstract

The present invention relates to novel macrocycles of general formula (I) and their use for the treatment of cancer diseases.



(I)